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► **To cite this version:**

Xi Wang, Ni Tang, Yanlong Hou, Abhishek S Prayag, Claude Gronfier, et al.. Daily Fluctuations vs Stability over days: A longitudinal analysis of Interoception and Physiological Markers. 2024. hal-04730520

**HAL Id: hal-04730520**

**<https://hal.science/hal-04730520v1>**

Preprint submitted on 10 Oct 2024

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# Daily Fluctuations vs Stability over days: A longitudinal analysis of Interoception and Physiological Markers

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## **Abstract**

Hunger and satiety, as two main interoceptions alternating around each meal, participate in the control of food intake. However, the temporal characteristics of these sensations across different times of the day and from one day to another, as well as their relationship with other physiological parameters, remain poorly understood.

In a five-day laboratory study, 20 healthy male participants ( $24.2 \pm 3.3$ ) received three meals (breakfast, lunch, dinner) at wake (WT) + 50 min, WT + 320 min, WT + 720 min, based on each individual's habitual sleep/wake times. Subjects were not allowed naps during the 16-h day, and their 8-h sleep at night was recorded with polysomnography. Questionnaires investigating hunger and satiety were given before and after each meal. Heart rate was measured continuously and glucose levels every 15 min.

We found that: 1) hunger and satiety of each individual showed a dynamic daily variation, with minimal hunger and satiety at breakfast and increasing levels throughout the day, reaching a maximum at lunch ( $p < 0.01$ ), and no difference between lunch and dinner; 2) the perception levels of hunger and satiety was subject dependent, and the levels were stable in each subject across the 5 experimental days ( $p < 0.0001$ ); 3) heart rate and glucose levels were significantly influenced by the day of the study, meal time, and internal state (pre/post-meal); 4) sleep duration and structure did not correlate with daytime interoception.

Altogether, our results reveal that hunger and satiety are two individual interoception modalities that are both dynamic during the day and remarkably stable throughout the week (in this 5-day experimental study). They suggest that hunger and satiety are robust in controlling food intake, and that good sleep optimizes energy balance, promotes optimal metabolic function, and maintains regular eating patterns.

**Key words:** dynamic, stability, hunger, satiety, interoception, sleep, rhythms, circadian

## 1. Introduction

Food intake is a regular and discontinuous behavior influenced by both interoception and exteroception (Bellisle, 2005; Berthoud, 2011). Interoception, the perception of the body's internal state, is one of the crucial factors used to maintain homeostasis and guide behavior to support the body needs (Craig, 2002). Exteroception, the ability to perceive external stimuli (such as vision, audition, olfaction, gustation, and somatosensation), allows us to process sensory information from outside environment of the body (Giromini et al., 2022), and form a conscious perception of the environment (Canu et al., 2021).

Hunger and satiety are the two most important interoceptions relative to food intake, which modulates eating behavior. Hunger is the body's natural response to energy deficiency, characterized by sensations such as a pit in the stomach, gurgling, or cramps, which signal to the brain that the body is running low on energy and requires calories. It is driven by the interaction between the central nervous system, peripheral signals, and hormonal pathways (Kojima et al., 1999; Schwartz et al., 2000; Woods et al., 1998). The stomach secretes the hormone ghrelin, and its concentration increases before meals. Additionally, a transient drop in blood glucose concentration often signals the onset of a meal (Campfield & Smith, 1990a, 1990b). In contrast, satiety signals the cessation of food intake, reflecting the satisfaction of metabolic needs (Bellisle, 2005; Woods et al., 1998). The post-meal satiety curve typically peaks 20-30 min after consumption (Holt et al., 1995). The alternation between hunger and satiety around the food intake reflects the body's homeostatic mechanisms aimed at maintaining energy balance and overall homeostasis (Bellisle, 2005; Blundell et al., 2010). However, hunger and satiety are also influenced by external factors, such as sensory, cognitive, sociocultural, and environmental, which determine the selection, quantity, quality, timing, frequency, and rhythm of food intake. (Bellisle, 2005; Berthoud et al., 2020; Broussard et al., 2016; Challet, 2019; Kabir et al., 2018; Marcelino et al., 2001; McNeil et al., 2017; Paoli et al., 2019).

The hypothalamus is crucial for coordinating the appropriate physiological and behavioral responses (Timper & Brüning, 2017). Notably, food intake, a fundamental physiological function, is closely related to the sleep-wake cycle, characterized by rhythmicity. The master circadian clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Leger et al., 2018; Moore & Eichler, 1972), controls peripheral clocks in most organs and tissues (such as liver, heart, stomach, muscles, adipose tissues, etc.), which are closely associated with maintaining energy balance (Balsalobre et al., 2000; Challet, 2009; Damiola et al., 2000; Davidson et al., 2002; Lamia et al., 2008; Paschos et al., 2012). Several studies have shown that circadian rhythms and meal timing impact eating behavior and energy balance in both animals and humans. Mice studies have demonstrated that a complete deletion of clock genes *Rev-erb $\alpha$*  (*Nr1d1*), attenuates day-night fluctuations in food consumption (Sen et al., 2018). When food is limited during the resting phase, the food clock drives changes in behavioral rhythms (Mistlberger, 2011), suggesting a potential intervention for metabolic health (Hatori et al., 2012). In humans, food consumption close to bedtime is often associated with higher weight status and more calorie intake (Baron et al., 2011; Garaulet et al., 2013; Xiao et al., 2019) suggesting that the timing of eating plays a crucial role in maintaining energy balanced metabolism, a misaligned eating time is increasingly becoming a risk for obesity (Boege et al., 2021). Moreover, previous studies have shown that hunger follows a dynamic 24-hour rhythm, with peak times either in the evening (Sargent et al., 2016) or in the morning (Qian et al., 2019; Scheer et al., 2013).

However, disruption of the circadian rhythm or sleep restriction, leading to changes in hormone levels and modified interoception (Scheer et al., 2009).

Hunger and satiety do not occur in isolation but are closely related to various physiological processes. The autonomic nervous system (Nederkoorn et al., 2000), which regulates heart rate (HR), is involved in the complex interactions that signal hunger and satiety to the brain. After a meal, increased HR is associated with parasympathetic nervous system activation, which promotes digestion and nutrient absorption (Harthoorn & Dransfield, 2008). Glucose levels also play a crucial role in energy homeostasis and are linked to hunger and satiety sensations. A decrease in blood glucose concentration typically triggers hunger signals, while increases in glucose levels contribute to feelings of satiety (Campfield et al., 1985; Campfield & Smith, 1990a; Louis-Sylvestre, 1976).

Sleep, another critical physiological function regulated by circadian rhythms, occurs at times opposite to food intake. Growing evidence has shown an intimate relationship between sleep patterns and food intake. Sleep influences metabolism and plays a key role in regulating appetite and eating behaviors (Depner et al., 2018; Markwald et al., 2013; McNeil et al., 2017, 2017; Spiegel et al., 1999, 2009). In addition, the relationship between sleep and obesity has become increasingly important in recent years, with evidence suggesting that sleep misalignment during daytime, or poor quality of sleep (Brondel et al., 2010; McHill et al., 2014; Spiegel et al., 2009) affect eating behaviors such as food selection, scheduling, and thus contributes to obesity (Antunes et al., 2010; Arble et al., 2009; Broussard & Van Cauter, 2016; Spaeth et al., 2013).

Even though hunger and satiety have been measured in many studies, few have explored these sensations over multiple meals throughout the day. Additionally, the question of whether an individual's interoception significantly varies from one day to another has not been thoroughly addressed. Light, as the primary cue that synchronizes the wake/sleep cycle, influences many physiological functions (Prayag, 2019, clock and sleep). Yet, how nocturnal light affects food intake by altering interoception (hunger and satiety) is still unclear. The aims of this study were to investigate 1) the characteristics of interoception (hunger and satiety) related to food intake, focusing on its evolution across the day and throughout the week, 2) the physiological patterns, such as heart rate, glucose levels, in relation to meals and over the week, and their relationship with interoception. 3) whether sleep patterns (total sleep time, sleep latency), influenced by low nighttime light and their relationship with interoception.

## **2. 2. Material and Methods and Materials**

### **2.1. Participants**

Twenty healthy male participants were recruited for a 5-day inpatient laboratory study (age  $24.2 \pm 3.3$ ). Each participant filled out several questionnaires about personal information, general health, sleep quality (Pittsburgh Sleep Quality Questionnaire, PSQI, (Buysse et al., 1989)), chronotype typology (Horne & Ostberg, 1976), and Munich Chronotype Questionnaire (MCTQ, (Roenneberg et al., 2003)), Beck Depression Inventory (BDI, (Beck et al., 1961)), and Eating Attitude Test (Garner & Garfinkel, 1979).

Participants' inclusion criteria were: PSQI score  $\leq 5$ , Horne & Ostberg chronotype score between 42 and 78, BDI score  $\leq 10$ , and Eating Attitude Test score  $\leq 20$ . Participants who had engaged in shift

work for the last two months (between 11 PM to 6 AM), or had transmeridian travel in the past month were excluded. Subjects were instructed to maintain a consistent sleep/ wake schedule for an average of 2 weeks prior to the laboratory session (with a deviation of less than 30 minutes from the target bed and wake times), and this was verified using both a daily sleep diary and an actimeter worn on the non-dominant wrist (ActTrust, Condor Instruments, São Paulo, Brasil). Participants also completed a light exposure diary, and a diet diary.

## **2.2. Study design**

Participants were admitted to the laboratory on Monday and were discharged on Friday evening (Fig.1a)

During the study, participants were in time-isolation conditions (deprived of any day-time indicators such as natural light, watches, clocks, TV, smartphone, radio). Naps were not permitted during the day, participants were not allowed to lie down on their bed, and their physical activity was restricted to walking about their room and stretching so as not to cause a significant increase in body temperature (more than 0.5 degrees Celsius).

Light intensity for both day and night was controlled. During the day, from waking up to bedtime, light intensity was maintained at 90 lux. During the night, from bedtime to wake-up time (a duration of 8 hours), low artificial light was set at one of four randomized light conditions: 0, 3, 8, 20 lux. Each participant was exposed to all four light conditions during the experiment session in the laboratory (one light condition per night). The order of light presentation was balanced according to a 4\*5 Latin square design.

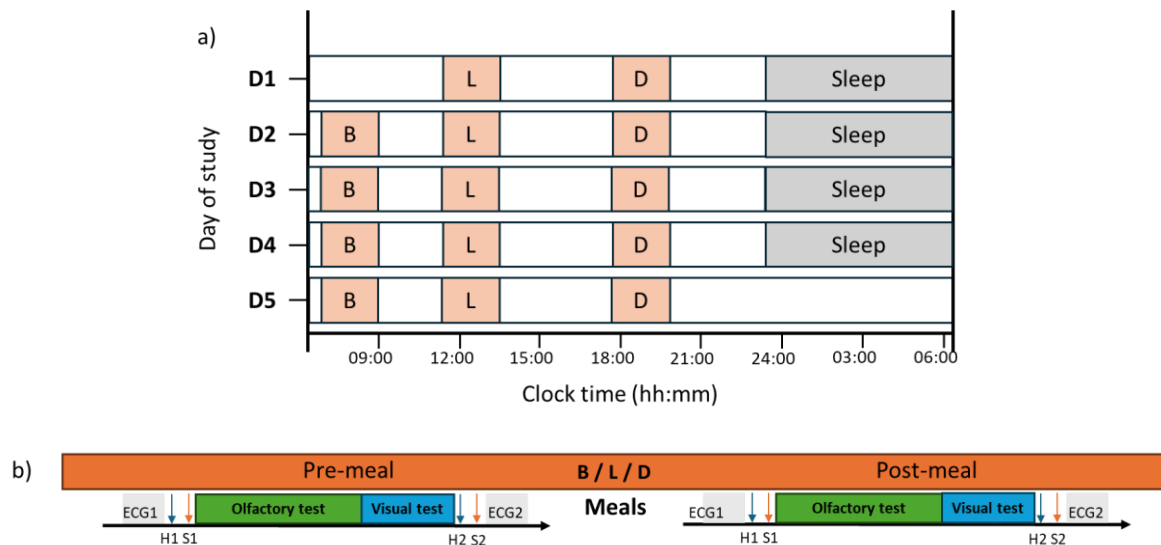
Sleep and mealtimes were calculated individually, based on each participant's habitual sleep-wake schedule. Habitual sleep times were calculated for each subject using the following procedure: 1) we averaged the bedtimes and waketimes of the last 7 sleep episodes (documented by each subject on their sleep diary), 2) we took the midsleep between the average bedtime and waketime, 3) we subtracted 4h to the midpoint to obtain the habitual bedtime, and we added 4h to the midpoint to obtain the habitual waketime (Daguet et al., 2022). Their mealtimes were calculated to be at habitual wake-up time (HWT) + 50 minutes for breakfast, HWT + 320 minutes for lunch, and HWT+ 720 minutes for dinner (corresponding to 07h50, 12h20, 19h00 for someone waking up at 07h00). For breakfast, participants could choose their first laboratory breakfast from a list provided on day 1, but they could not change their selection after that decision (from Wednesday), neither the quantity nor the type of food, so that each breakfast was the same. Lunch and dinner were provided by the hospital cafeteria, with the menu changing quarterly. The standard meal consisted of an appetizer (70 - 100 g), a main course (meats/fish/egg with vegetables,  $407 \pm 59$  g), a side dish (rice/noodles with bread,  $173 \pm 60$  g), a dessert ( $128 \pm 41$  g), and a dairy product ( $81 \pm 42$  g). Participants were informed they could stop eating when feeling satiated.

## **2.3. Tests**

During the daytime, sensory olfactory and visual tests were performed six times per day, once 15 minutes before and once 20 minutes after meal (Fig. 1b), with this pattern repeated throughout the

entire study. They lasted for 10 (breakfast)/ 20 (lunch and dinner) minutes each time. Participants were seated 60 cm in front of the test screen, with communication through an interphone. All sensory tests and instructions were provided via the Superlab software (Cedrus, San Pedro, CA, version 5.0). The tests consisted in olfactory and visual tests using the same stimuli in both pre- and post-meal conditions. The pre- and post-meal tests began with a one-minute baseline recording, during which participants were asked to remain calm and motionless while HR was recorded using two electrodes placed at V1 and V6 on the chest.

Self-assessment of hunger and satiety were conducted just before and just after each sensory tests, using a computerized Visual Analog Scale (VAS).



**Figure 1.** Illustration of the 5-day experimental protocol in the laboratory. **a)** Subjects arrived on Monday, two hours after their habitual waketime, and were discharged on Friday (at habitual bedtime). Three meals were provided per day (except Monday because subjects arrived after breakfast at home): breakfast (B), lunch (L), and dinner (D). Sleep times were scheduled at each subject’s habitual sleep times; here bedtimes and waketimes are set at 2334 and 0734 respectively (mean  $\pm$  SD: 23:34 $\pm$ 00:47). **b)** Sensory tests were conducted 15 minutes before breakfast, and 30 minutes before lunch and dinner. Participants commenced with a one-minute electrocardiogram (ECG1) measurement, followed by an assessment of hunger (H1) and satiety (S1). Next, participants underwent olfactory and visual tests. At the end of the test, a new self-evaluation of hunger (H2) and satiety (S2) was performed, and a final one-minute ECG-2 was taken. The post-meal test was performed 20 minutes after the meal and followed the same procedure as the pre-meal test.

## 2.4. Measures

### Subjective measures

Hunger and satiety levels were self-assessed using a Visual Analog Scale (VAS). A 30 cm long line was displayed on the screen (51\*29 cm), with the left side representing “not hungry at all”, or “not satiated at all”, and the right side representing “extreme hunger” or “extreme satiated”. Participants were required to click on the lines to indicate their momentary sensations of hunger or satiety. The click points on the VAS were converted into a numerical scale from 0 and 15, with 0 representing the left most point and 15 representing the rightmost point.

### **Heart rate**

Heart rate (HR) was recorded at a frequency of 256 Hz using a polysomnography (PSG) monitoring system - Vitaport 4 software (Vitaport-4 digital recorder, TEMEC Instruments, Kerkrade, Netherlands). Two electrodes, one positive and one negative, were placed on the thoracic at positions V1 and V6 respectively. HR was recorded for one minute before and one minute after the sensory test. The mean HR during each recording period was calculated.

### **Glucose**

Glucose concentrations were recorded using a continuous glucose monitoring (CGM) system (FreesStyle Libre2). The CGM sensor was applied on the back of the upper glucose levels were obtained every 15 minutes during the entire 5-days study.

### **Sleep**

Sleep polysomnography was recorded every night from before habitual bedtime to after habitual waketime (Vitaport-4, digital recorder, TEMEC Instruments, Kerkrade, Netherlands). Four EEG (electroencephalogram) electrodes were placed on the scalp on the C3, C4, O1, and O2 sites according to the 10-20 international system, and referenced to their contralateral mastoids (A1, A2). Two EOG (electrocardiogram) electrodes were placed at 1 cm of the external canthus of the eyes and crossed-referenced. Three EMG (electromyogram) were placed on the chin muscle (upper right, upper left, lower center) and cross-referenced (left-center and right-center). All signals were filtered using a high-pass filter at 0.3 Hz, a low-pass filter at 45 Hz, a notch filter at 50 Hz, and recorded at sampling rate of 256 Hz.

### **Ethics**

All experimental procedures were conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board (Comité de Protection des Personnes, Lyon, France, N°ID-RCB: 2023-A01561-44). All participants signed their information and consent forms.

## **2.5. Statistical analysis**

Statistical analyses were conducted using RStudio ((Posit), version 2023.06.2, PBC, Boston, MA, USA)). All analyses (hunger, satiety, heart rate, blood glucose, total sleep duration time (TST), and sleep latency (SL), were based on raw data. To eliminate the “first day effect” on eating and behavior, analyses were conducted from Tuesday (Day 2) to Friday (Day 5), with data collected before/after each of the three daily meals.

To ensure the integrity of the dataset and the reliability of the analysis, outliers were systematically identified and removed using a robust statistical approach. Specifically, the detection of outliers was based on the interquartile range (IQR) method, in which outliers were defined as data points that fell outside the acceptable range, specifically below the first quartile ( $Q1 - 1.5 * IQR$ ) or above the third



quartile ( $Q3 + 1.5 * IQR$ ). Once the outliers were identified, they were excluded from subsequent analyses.

To investigate whether interoception (hunger, satiety) was influenced by the time of day (breakfast, lunch, dinner), we separated hunger and satiety based on the pre- or post-meal conditions and applied a linear mixed-effects model. For example, the model specification for hunger in the pre-meal condition was as follows: 1) *PreHunger <- lme (Hunger ~ Mealtime, random = ~1|participants)*. This model analyzed the relationship between the dependent variable “Hunger” and the fixed effects “Mealtime”. The *random = ~1|Participant* specifies that participants were considered as a random factor, allowing hunger levels to vary across individuals due to individual differences (Cheon & Mattes, 2024; Ruddick-Collins et al., 2019; Stevenson et al., 2015). After fitting the model, we analyzed the variances (ANOVA) with a repeated measure approach to test the significance of the fixed effects (Mealtime) in explaining the variability of the hunger scores. The same analyses were performed for post-meal hunger, pre-meal satiety, and post-meal satiety, as well as physiological parameters (heart rate, glucose).

To examine the how interoception changed from one day to another, we adjusted the previous linear mixed models as follow: 2) *PreHunger <- lme (Hunger ~ Day, random= ~1|Participant)*. We then created three additional models for post-meal hunger, pre-meal satiety, and post-meal satiety, as well as physiological parameters.

We used the F-test to compare intra-subject (within-subject) variability over the week with inter-subject (between-subject) variability during the week.

To better understand the relationship between interoception (hunger, satiety), and its connection to physiological parameters (HR, glucose), both correlation tests and linear mixed-effects models were applied. The Spearman coefficient ( $r$ ) was used to quantify the strength and direction of the linear association between variables. Linear mixed models were employed to identify which factors - such as hunger, satiety, day, or meal - could predict the dependent variable.

The relationship between sleep and interoception was analyzed using Spearman’s correlation as the hunger and satiety scores were not normally distributed. Correlations were tested between sleep patterns - such as total sleep time (TST) and sleep latency (SL) - from the previous night (e.g., Tuesday night) and interoception (hunger, satiety) on the following day (corresponding to Wednesday). Analyses were performed both separately for light, day, and meal conditions, as well as across the overall dataset.

All findings were considered statistically significant when  $p < 0.05$ . Data are presented as the mean  $\pm$  standard error of the mean (SEM) in the graphs.

### 3. Results

#### 3.1. Fluctuation of interoception during the day

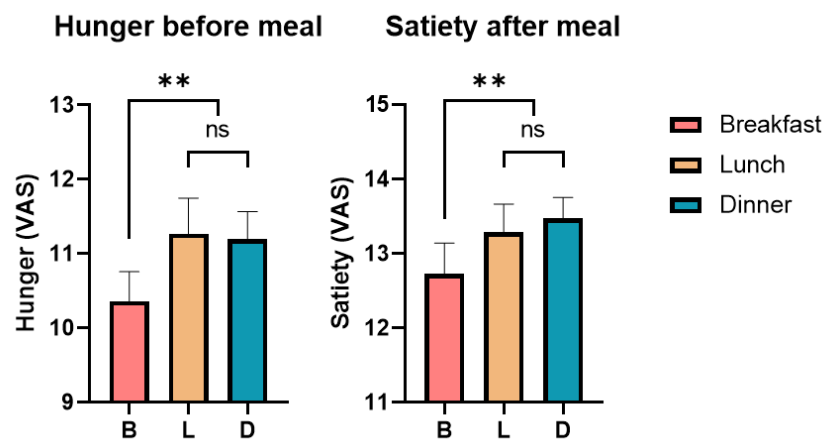
The linear mixed-effects model revealed a significant main effect of meals on hunger levels before mealtime ( $F(2, 206) = 8.43, p < 0.0001$ ). Post hoc comparison showed that pre-meal hunger significantly increased at lunch ( $11.25 \pm 0.4, p < 0.001$ ) and dinner ( $11.19 \pm 0.4, p < 0.001$ ) compared to breakfast ( $10.37 \pm 0.4$ ), with no significant difference between lunch and dinner.

Satiety displayed a significant main effect of mealtime throughout the day in post-meal conditions ( $F(2, 208) = 7.56, p < 0.0001$ ). Post hoc comparison revealed that satiety was significantly higher at lunch ( $13.4 \pm 0.34, p < 0.001$ ) and dinner ( $13.5 \pm 0.34, p < 0.001$ ) compared to breakfast ( $12.93 \pm 0.34$ ), with no difference between lunch and dinner (Fig. 2, Fig 3).

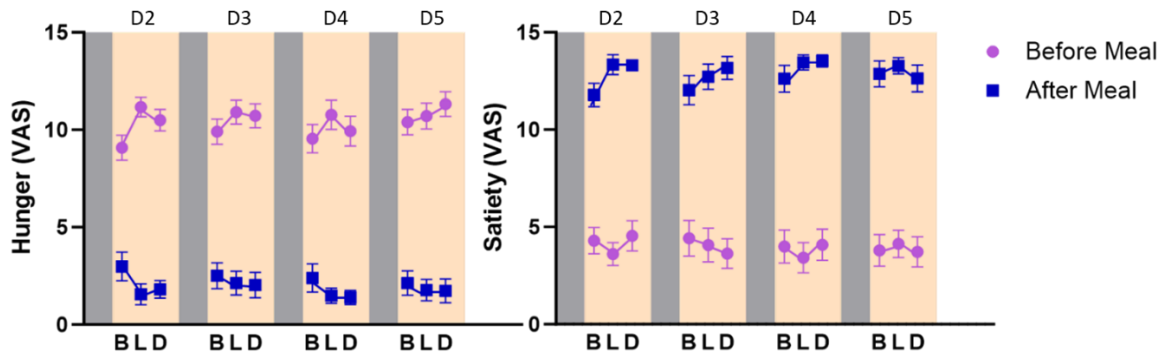
### 3.2. Stability of interoception throughout the week

The dynamics of hunger and satiety pre- and post-meal are illustrated in fig. 2 and fig. 3. The linear mixed regression analyses showed no statistical differences among the 4 days for both pre-and post-meal hunger and satiety measurements. Pre-meal hunger did not show any significant difference throughout the day ( $F(3, 205) = 1.68, p > 0.05$ ), with pre-meal hunger values ranging from 9.59 (Day 2) to 10.77 (Day 5) at breakfast, 11 (Day 2) to 11.49 (Day 5) at lunch, and 10.81 (Day 2) to 11.71 (Day5). Similarly, post-meal hunger did not show any difference ( $F(3, 200) = 0.62, p > 0.05$ ), with post-meal hunger values ranging from 1.76 to 2.25 at breakfast, 1.15 to 1.59 at lunch, and 1.36 to 1.68 at dinner. Pre-satiety hunger also remained stable ( $F(3, 217) = 0.44, p > 0.05$ ), with pre-meal satiety values between 3.79 to 4.42 at breakfast, 3.41 to 4.13 at lunch, and 3.63 to 4.54 at dinner, and post-meal satiety remained constant ( $F(3, 207) = 1.21, p > 0.05$ ), ranging from 12.3 to 13.3 at breakfast, 13 to 13.6 at lunch, and 13.3 to 13.5 at dinner (Fig. supplementary 1).

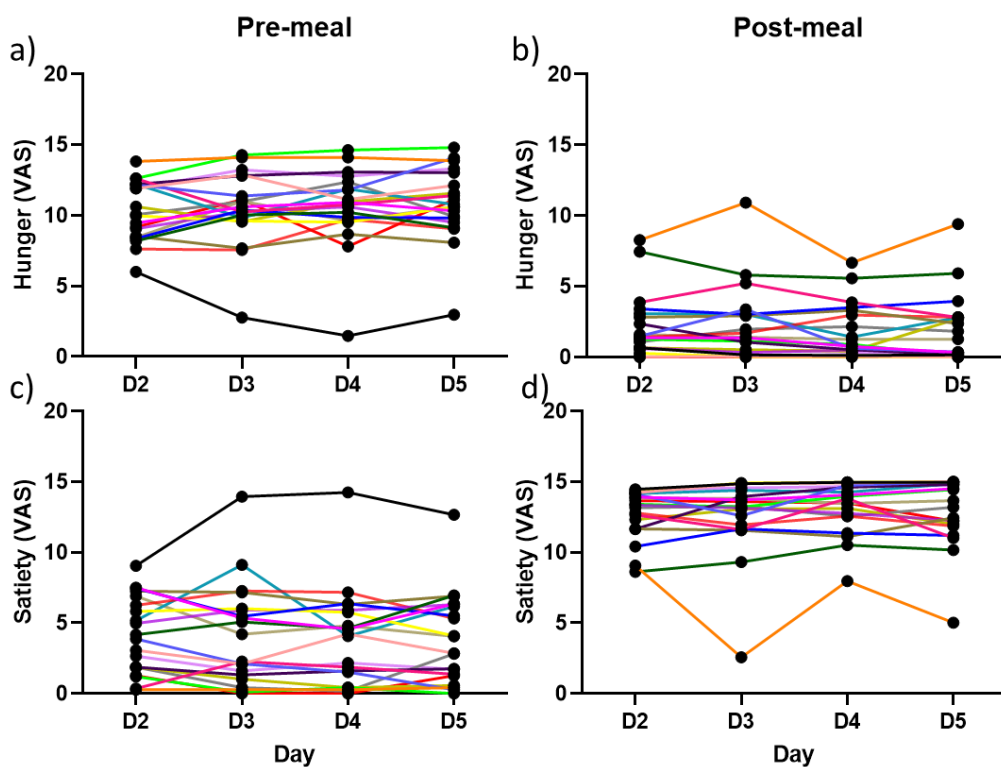
Additionally, the F-test results revealed that within-subject (intra-subject) variability in hunger levels was significantly lower than between-subject variability (inter-subject) in both pre-meal condition [ $F(76,60) = 10.50, p < 0.0001$ ] (Fig. 4a), and post-meal condition [ $F(76,60) = 15.38, p < 0.0001$ ] (Fig. 4b). Similarly, for satiety, the variability between subjects was lower than within subjects, with significant differences in both the pre-meal condition [ $F(76,60) = 13.54, p < 0.0001$ ] (Fig. 4c) and post-meal condition [ $F(76,60) = 9.37, p < 0.0001$ ] (Fig. 4d). (The same data illustrated in different formats in Fig. Supplementary 2).



**Figure 2** : Dynamic hunger before meal and satiety after meal throughout the day with measurements taken at breakfast (B), lunch (L), and dinner (D). Data are presented as the mean  $\pm$  SEM in the graphs.



**Figure 3.** Hunger and satiety levels before and after meals over 4 days (D2 to D5) with measurements taken at breakfast (B), lunch (L), and dinner (D) times. Data are presented as the mean  $\pm$  SEM in the graphs.



**Figure 4.** Stability of individual hunger and satiety throughout the experimental study from D2 (Day 2) to D5 (Day 5). Each point represents the average values of three meals (breakfast lunch and dinner), and each line corresponds to one participant's raw data.

### 3.3. Physiological parameters

#### 3.3.1. Heart rate

##### Heart rate as a function of meal and time of day

Pre-meal HR demonstrated a significant mealtime effect ( $F(2, 218) = 18.51, p < 0.0001$ ). Breakfast showed the highest pre-meal HR ( $66.4 \pm 1.86$  bpm), which was significantly higher compared to lunch

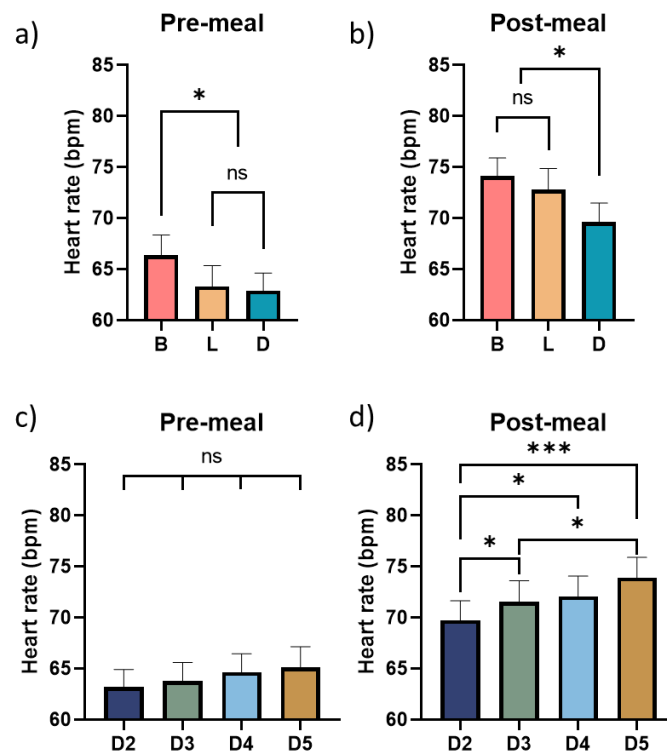
( $63.3 \pm 1.86$  bpm) and dinner ( $62.9 \pm 1.86$  bpm). There was no significant difference in pre-meal HR between lunch and dinner (Fig. 5a).

Post-meal HR also exhibited a significant mealtime effect ( $F(2, 217) = 22.8, p < 0.0001$ ). Post-hoc analysis revealed that HR after dinner ( $69.6 \pm 1.93$  bpm) was significantly lower than HR after breakfast ( $73.4 \pm 1.93$  bpm) and lunch ( $72.8 \pm 1.953$  bpm), with no significant difference between breakfast and lunch (Fig. 5b).

### Heart rate as a function of the experimental day

Pre-meal HR remained stable throughout the experiment day, showing no significant differences from Day 2 to Day 5 ( $F(3, 217) = 2.62, p > 0.05$ ), with HR approximately 63 to 65 beats per minute (bpm)(Fig. 5c).

Post-meal HR showed significant changes over the day of the week ( $F(3, 216) = 10.34, p < 0.0001$ ). A progressive increase in HR was observed, starting at  $69.8 \pm 1.95$  bpm on Day 2 and rising to  $73.8 \pm 1.95$  bpm on Day 5. Post-hoc analysis using Bonferroni correction revealed that Day 2 was significantly lower than on the other days (all  $p < 0.05$ ), and Day 3 ( $71.8 \pm 1.95$  bpm) was lower than Day 5 ( $p < 0.05$ ). No significant differences were observed between Day 3 and Day 4 ( $72.3 \pm 1.95$  bpm) or between Day 4 and Day 5 ( $p > 0.05$ ). (Fig. 5d).



**Figure 5.** HR across days and in response to mealtime. HR evolution was examined in relation to mealtime, with measurements taken both pre-meal (5a) and post-meal (5b) at B (breakfast), L (lunch), and D (dinner). HR across the experiment day, from D2 (Day 2) to D5 (Day 5) at both pre-meal (5c) and post-meal (5d). Data are presented as the mean  $\pm$  SEM in the graphs.

### 3.3.2. Glucose

#### Glucose as a function of meal and time of day

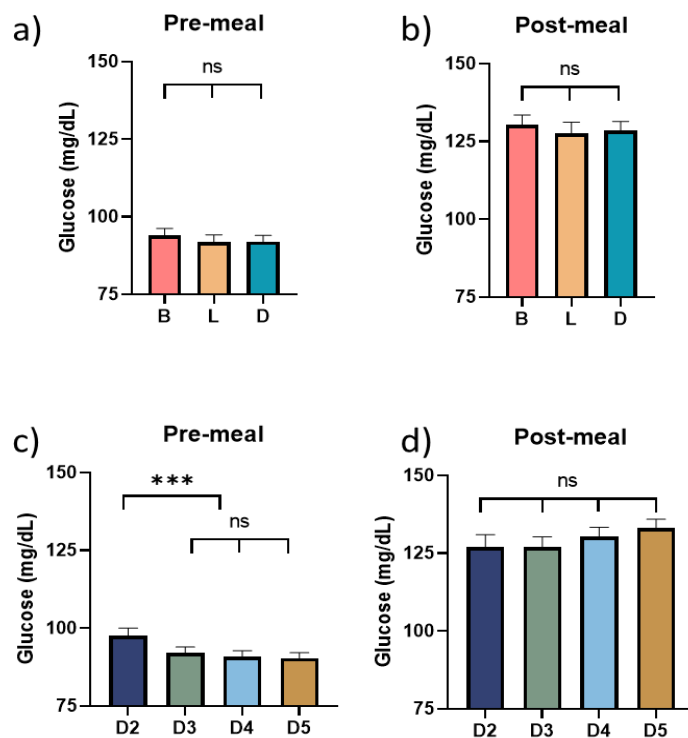
Pre-meal glucose levels were relatively stable across different mealtimes ( $F(2, 214) = 1.80, p > 0.05$ ), with glucose ranging from 92 to 94 mg/dL (Fig. 6a).

Post-meal glucose levels remained similar stability as pre-meal levels ( $F(3, 212) = 1.30, p > 0.05$ ) with glucose approximately 128 to 131 mg/dL (Fig. 6b).

#### Glucose as a function of experimental day

Pre-meal glucose levels demonstrated a significant day effect ( $F(3, 213) = 15.08, p < 0.0001$ ). Post-hoc analysis pairwise comparisons with Bonferroni correction revealed that glucose levels on Day 2 ( $97.9 \pm 2.04$  mg/dL) were significantly higher compared to Day 3 ( $92.2 \pm 2.03$  mg/dL), Day 4 ( $90.8 \pm 2.03$  mg/dL), and Day 5 ( $90. \pm 2.03$  mg/dL) (all  $p < 0.0001$ ) (Fig. 6c).

Post-meal glucose levels showed stability performance throughout the week, with no significant difference between days ( $F(3, 211) = 2.55, p > 0.05$ ), ranging from 126 to 133 mg/dL (Fig. 6d).



**Figure 6.** Glucose levels before and after meals, and across experimental days. Glucose is shown pre-meal (a) and post-meal (b), at B (breakfast), L (lunch), and D (dinner). Glucose is shown across the experimental days, from Day 2 (D2) to Day 5 (D5), both pre-meal (c) and post-meal (d). Data are presented as the mean  $\pm$  SEM in the graphs.

### **3.4. Correlations**

#### **3.4.1. Correlation between interoception markers (hunger and satiety)**

To better understand the relationship between hunger and satiety, we conducted a correlation test. Pre-meal hunger was negatively correlated with pre-meal satiety ( $r = -0.68$ ,  $p < 0.0001$ ), and post-meal hunger was negatively correlated with post-meal satiety ( $r = -0.86$ ,  $p < 0.0001$ ). However, no significant correlation between pre-meal hunger and post-meal satiety ( $r = 0.02$ ,  $p > 0.05$ ), when analyzed separately by day or light, and meal conditions.

#### **3.4.2. Correlation between interoception and physiological parameters**

##### **Interoception with heart rate (HR)**

In the pre-meal condition, no significant linear correlation was found between pre-meal hunger and HR ( $r = -0.04$ ,  $p > 0.05$ ), nor between pre-meal satiety and HR ( $r = -0.04$ ,  $p > 0.05$ ). However, a linear mixed analysis revealed a significant relationship between pre-meal HR and hunger ( $F(1, 204) = 4.11$ ,  $p = 0.04$ ), as well as between pre-meal HR and day ( $F(3, 204) = 3.27$ ,  $p = 0.02$ ). No significant relationship was observed between pre-meal satiety and HR.

In the post-meal condition, a significant linear correlation was found between post-meal satiety and HR ( $r = 0.14$ ,  $p < 0.05$ ), but no significant correlation was observed between post-meal hunger and HR. A linear mixed analysis revealed significant relationships between post-meal HR and hunger ( $F(1, 196) = 6.78$ ,  $p < 0.01$ ), day ( $F(3, 196) = 12.79$ ,  $p < 0.0001$ ), and meal ( $F(3, 198) = 10.69$ ,  $p < 0.0001$ ).

##### **Interoception with Glucose levels**

In the pre-meal condition, no significant linear correlation was observed between glucose levels and hunger ( $r = 0.001$ ,  $p > 0.05$ ) or satiety ( $r = -0.04$ ,  $p > 0.05$ ). However, a linear mixed model revealed significant relationships between pre-meal glucose and pre-meal hunger ( $F(1, 200) = 8.64$ ,  $p < 0.01$ ) as well as day ( $F(3, 200) = 12.22$ ,  $p < 0.0001$ ). In addition, a significant relationship was observed between pre-meal glucose and pre-meal satiety ( $F(1, 212) = 7.02$ ,  $p < 0.001$ ) and day ( $F(3, 212) = 14.8$ ,  $p < 0.0001$ ).

In the post-meal condition, a significant linear correlation was found between hunger and glucose ( $r = 0.17$ ,  $p < 0.01$ ), but no significant correlation was observed between satiety and glucose ( $r = -0.04$ ,  $p > 0.05$ ). The linear mixed model did not show significant relationships between post-meal glucose and either hunger ( $p > 0.05$ ) or satiety ( $p > 0.05$ ).

##### **Interoception with sleep duration**

Spearman correlation tests were applied to examine the relationship between sleep patterns and interoception. Total sleep time (TST) did not significantly correlate with pre-meal hunger, post-meal hunger, pre-meal satiety, or post-satiety (all  $p > 0.05$ ) when analyzed separately by light, day, and

meal conditions. Similarly, no significant correlation was observed between sleep latency (SL), and any interoception across these same conditions (all  $p > 0.05$ ).

However, when analyzing the entire data, pre-meal hunger showed a significant positive correlation with TST ( $r = 0.24$ ,  $p < 0.001$ ) and a negative correlation with SL ( $r = -0.16$ ,  $p < 0.05$ ). Pre-meal satiety was negatively correlated with TST ( $r = -0.14$ ,  $p < 0.05$ ) and positively correlated with SL ( $r = 0.26$ ,  $p < 0.001$ ).

#### 4. Discussion

The current study examines the characteristics of interoception related to food intake, using a highly controlled five-day laboratory protocol in which hunger and satiety were measured before and after each meal for 14 consecutive meals. Our results showed that interoception: 1) fluctuates during the day, 2) this fluctuation during the day is similar across days, 3) hunger and satiety are regulated by distinct mechanisms, 4) is not a simple covariate of heart rate, glucose and prior sleep duration.

Although both hunger and satiety were measured before and after each meal, as discussed below, only pre-meal hunger and post-meal satiety were discussed.

**Dynamic of interoception during the day.** Hunger and satiety are momentary sensations that reflect the body's current metabolic and energy states, particularly the empty or full states of the stomach. Hunger typically increases before a meal and diminishes afterward, while satiety shows the opposite pattern. However, we found that these sensations vary depending on the mealtime. Specifically, both pre-meal hunger and post-meal satiety are lower at breakfast compared to lunch or dinner. This suggests that hunger and satiety signals fluctuate throughout the day, with smaller signals in the morning (around breakfast) and stronger signals at midday (around lunch) and in the evening (around dinner).

This daily variation aligns with several circadian studies that have shown a similar pattern for hunger: a weaker hunger signal at the start of the day and a stronger one later in the day patients (Cugini et al., 1998; Fatati et al., 2001; Qian et al., 2019; Reichenberger et al., 2018; Sargent et al., 2016; Scheer et al., 2013). However, fewer studies have examined the daily variation in satiety. One exception is the study by Sargent et al. (2016), which measured both hunger and satiety in a 28-hour shifted protocol. Contrary to our findings, their study found the lowest satiety in the evening and the highest at the end of the night, with lower satiety in the morning. This discrepancy could be attributed to their methodology, as they measured hunger and satiety at the same time. Our results indicate a negative correlation between hunger and satiety when assessed simultaneously.

To capture satiety with physiological relevance, it is more appropriate to measure satiety after food ingestion or following a meal state (Benelam, 2009; Gibbons et al., 2019), as satiety typically peaks 15 minutes to 1 hour post-meal (Holt et al., 1995; Stubbs et al., 1993). The heightened pre-meal hunger and post-meal satiety later in the day may have evolutionary significance. These stronger signals could encourage increased food intake to ensure sufficient energy for the upcoming sleep period. However, in today's obesogenic environment, this pattern may represent a vulnerability, potentially leading to overeating.

**Stability of interoception from one day to another.** Although interoception varies throughout the day in relation to mealtime, our findings also indicate that it remains stable across the four days of the study. Each participant exhibited consistent hunger levels before breakfast, lunch, and dinner, with intra-individual variability significantly lower than inter-individual variability. In other words, the differences in interoception between individuals were far greater than the fluctuations experienced by the same individual over time.

While several studies have measured hunger or fullness (satiety) over multiple days or weeks (Cheon & Mattes, 2024; Ruddick-Collins et al., 2019; Stevenson et al., 2015), few have specifically investigated changes in interoception over time. Only the study of Cheon and Mattes (2024) observed that hunger and fullness were relatively stable when comparing measurements taken from weeks 1, 9, and 17. They also noted considerable variability between individuals, aligning with our results.

Moreover, the observed stability of interoception in our study is unlikely to be due to habitual use of the line scale. Participants were able to report lower hunger and satiety levels at the start of the day, with increased ratings at midday and dinner. Given that hunger and satiety are regulated by stomach fullness and hormones such as ghrelin and leptin (Cummings et al., 2001; Klok et al., 2007), the consistency of interoception across days may also reflect stable individual hormone secretion patterns (Scheer et al., 2009).

These findings suggest that the daily fluctuations in hunger and satiety are specific, stable characteristics that differentiate individuals based on their levels of interoception. This personal hunger and satiety perception may result from long-term physiological adjustments, which help maintain consistent food intake and body weight over time.

### **Hunger and satiety are two distinct parameters to interpret interoception related to food intake.**

Hunger and satiety are usually considered as negatively correlated parameters that reflect metabolic states, specifically the lack or fullness of energy. Consequently, in most studies, either hunger or satiety is measured in isolation. When both are assessed, they are often measured simultaneously (Scheer et al., 2013). Indeed, measuring hunger and satiety at the same time frequently reveals a statistically significant negative correlation. However, is it necessary to measure both hunger and satiety? What is the best method for assessing them?

Hunger and satiety function under different physiological conditions, utilizing distinct neural circuits and neurotransmitters to trigger varying behaviors (Amin & Mercer, 2016; Campfield & Smith, 1990b, 1990a; Cummings, 2006; Cummings et al., 2001; Schwartz et al., 2000). Therefore, measuring both parameters is essential, as they reflect different neural realities (Amin & Mercer, 2016; Nakamura & Nakamura, 2018). Our results indicate an absence of correlation between pre-prandial hunger and postprandial satiety, suggesting that pre-prandial hunger cannot predict postprandial satiety. These findings lead us to conclude that hunger and satiety represent two distinct events—intimately linked yet also independent of one other. Therefore, it is crucial to measure both parameters in their physiologically significant contexts: hunger before a meal and satiety after a meal.



### **Interoception and other physiological parameters.**

Even though several physiological parameters showed stability over the day or similar variation throughout the mealtime during the day, general results indicate an absence of correlation between interoception and these physiological parameters. This finding is not entirely surprising, as physiological parameters typically reflect a biological system's reaction to the presence of a stimulus, while interoception reflects different metabolic states. However, we observed some nuanced correlations; for instance, post-meal satiety exhibited a statistically significant positive correlation with heart rate. More detailed analyses are currently underway.

## **5. Conclusion**

From the data presented, we conclude that: 1) Hunger and satiety are the two interoceptions that may in concert but are distinct and independent from one another. 2) Each individual possesses their own perceived levels of hunger and satiety, which tend to be stable over relatively long periods. 3) During the day, perceived levels of both hunger and satiety fluctuate, with lower intensities during the beginning of the day and stronger around noon and dinner. 4) The relationship between interoception factors is complex, as it often incorporates multiple variables in regression models.

## **6. Author contributions**

TJ and CG designed the experiments. XW, ASP, NT, YH, CG, TJ collected the data. NT and YH analyzed the sleep data, and XW analyzed the sensory and physiological parameters. XW, TJ and CG interpreted the data and wrote the manuscript. NT, YH, ASP provided edits.

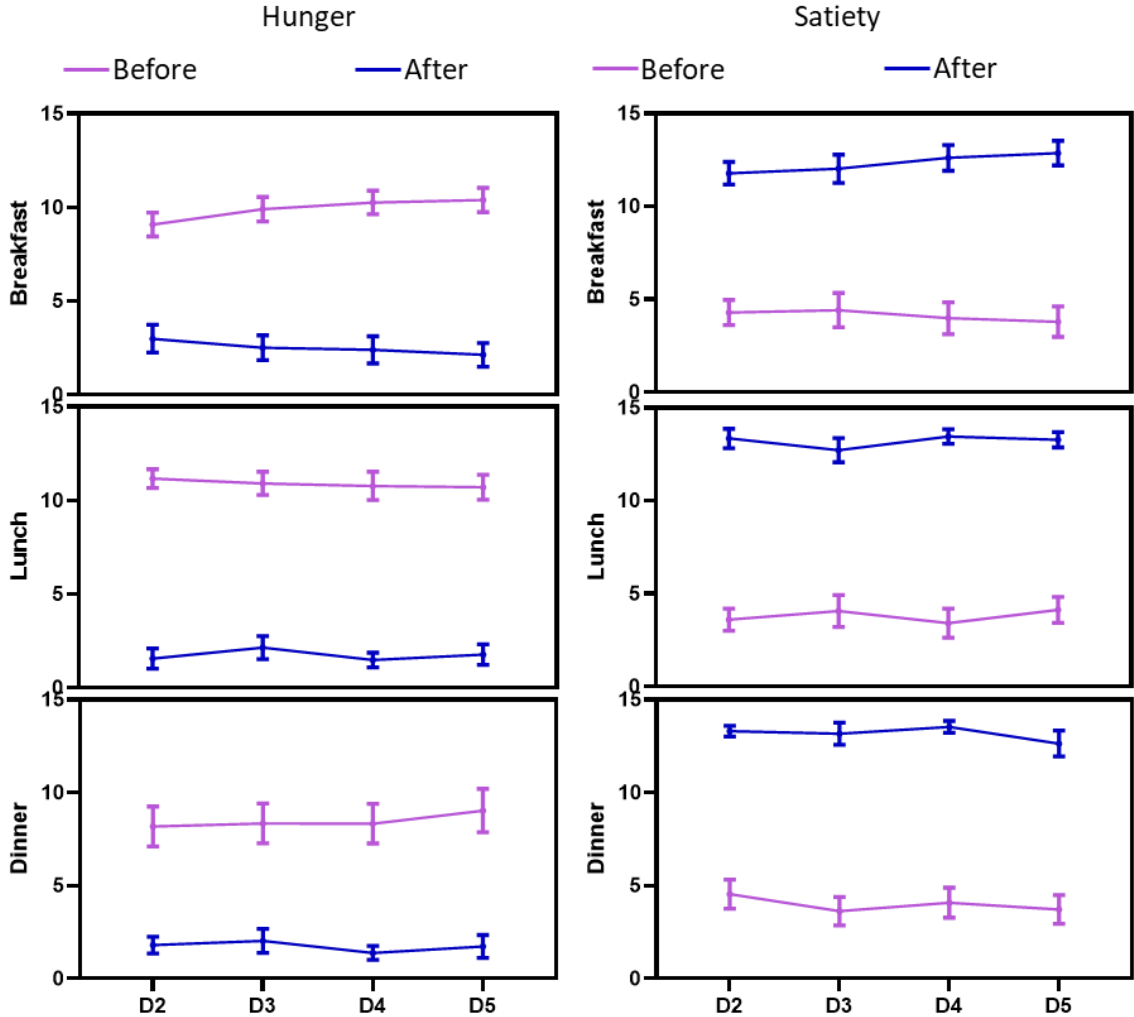
## **7. Funding**

This work was supported by grants from ANR (Idex Breakthrough ALAN), the University of Lyon (Rectolux) to CG, and funds from Inserm and CNRS to CG and TJ.

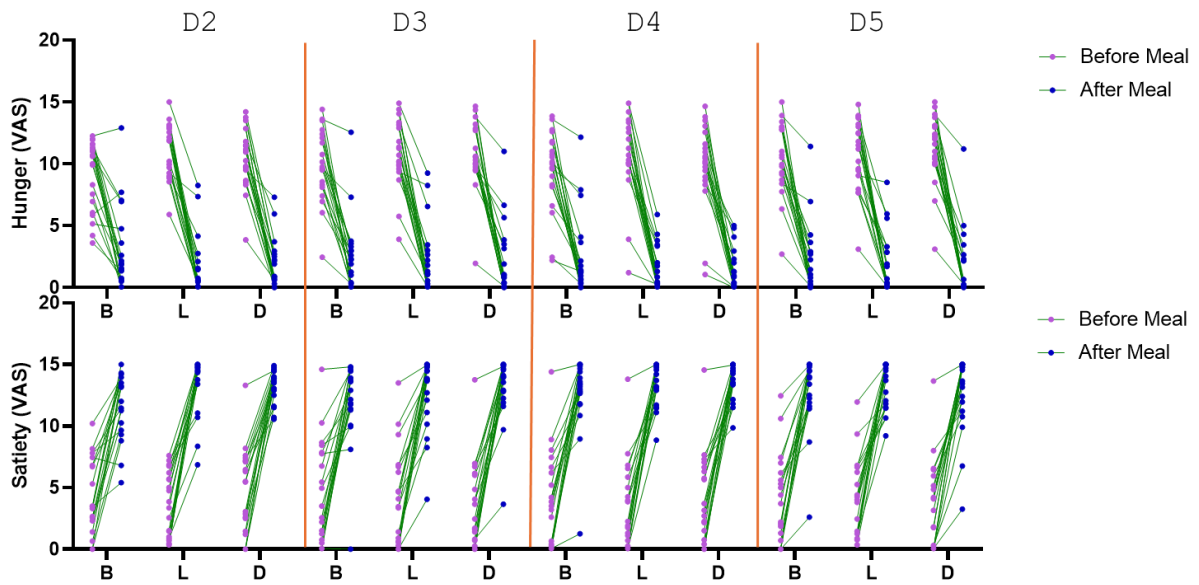
## **8. Acknowledgments**

The authors thank Anissa DAHMANI, and Lydie MERLE for their contribution to the study. The authors thank Marc THEVENET for his technical assistance, code writing, and help with data acquisition and data analysis. Finally, the authors would like to thank all the participants who were interested or participated in this study.

Supplementary informations:



**Supplementary figure 1.** Stability of hunger and satiety before and after meals over four days (D2 to D5), with measurements taken at breakfast, lunch, and dinner times. The pink line represents the mean of the pre-meal measurements, while the blue line represents the mean of the post-meal measurements. Error bar was represented by SE.



**Supplementary figure 2.** Hunger (top panel) and satiety (bottom panel) before and after each meal, measurements taken at breakfast (B), lunch (L), and dinner (D) times, across consecutive 12 meals from Day 2 to Day 5. Each line represents the measurements for one subject, with pink dots indicating pre-meal sensation and blue dots representing post-meal sensations.

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